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1: J Neurochem. 2004 May;89(3):581-92.

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The nerve growth factor precursor proNGF exhibits neurotrophic activity but is less active than mature nerve growth factor.

Fahnestock M, Yu G, Michalski B, Mathew S, Colquhoun A, Ross GM, Coughlin MD.

Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada. fahnest@mcmaster.ca

Nerve growth factor (NGF) promotes neuronal survival and differentiation and stimulates neurite outgrowth. NGF is synthesized as a precursor, proNGF, which undergoes post-translational processing to generate mature beta-NGF. It has been assumed that, in vivo, NGF is largely processed into the mature form and that mature NGF accounts for the biological activity. However, we recently showed that proNGF is abundant in CNS tissues whereas mature NGF is undetectable, suggesting that proNGF has biological functions beyond its role as a precursor. To determine whether proNGF exhibits biological activity, we mutagenized the precursor-processing site and expressed unprocessed, cleavage-resistant proNGF protein in insect cells. Survival and neurite outgrowth assays on murine superior cervical ganglion neurons and PC12 cells indicated that proNGF exhibits neurotrophic activity similar to mature 2.5S NGF, but is approximately fivefold less active. ProNGF binds to the high-affinity receptor, TrkA, as determined by cross-linking to PC12 cells, and is also slightly less active than mature NGF in promoting phosphorylation of TrkA and its downstream signaling effectors, Erk1/2, in PC12 and NIH3T3-TrkA cells. These data, coupled with our previous report that proNGF is the major form of NGF in the CNS, suggest that proNGF could be responsible for much of the biological activity normally attributed to mature NGF in vivo.

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